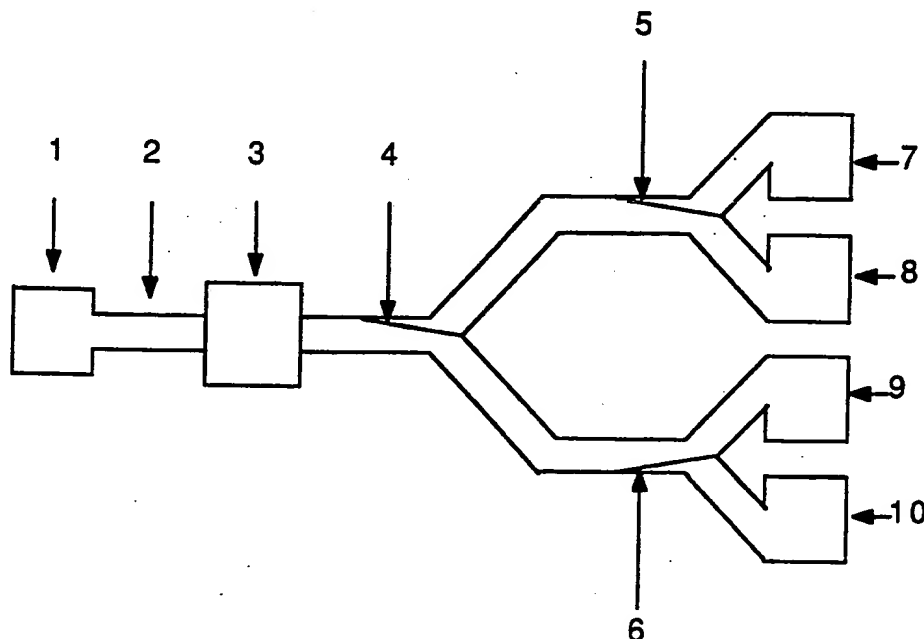




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : G01N 15/14, 15/02, B07C 5/342	A1	(11) International Publication Number: WO 91/15750 (43) International Publication Date: 17 October 1991 (17.10.91)
(21) International Application Number: PCT/GB91/00542 (22) International Filing Date: 8 April 1991 (08.04.91) (30) Priority data: 9008044.1 9 April 1990 (09.04.90) GB (71) Applicant (for all designated States except US): CARRI-MED LTD. [GB/GB]; Carri-Med House, Glebelands Centre, Vincent Lane, Dorking, Surrey RH4 3YX (GB). (72) Inventors; and (75) Inventors/Applicants (for US only) : KAYE, Paul, Henry [GB/GB]; TRACEY, Mark, Christopher [GB/GB]; Hatfield Polytechnic, College Lane, Hatfield, Herts. AL10 9AB (GB).		(74) Agent: MAURY, Richard, Philip; Sommerville & Rush-ton, 11 Holywell Hill, St. Albans, Herts. AL1 1EZ (GB). (81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB, GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent), US. Published <i>With international search report.</i>

(54) Title: MICROFABRICATED DEVICE FOR BIOLOGICAL CELL SORTING**(57) Abstract**

Apparatus for sorting cells into spatially separate sub-groups, comprising a microfabricated moveable structure (4, 5, 6) for directing cells between distinct spatial locations.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MG	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MN	Mongolia
BE	Belgium	GA	Gabon	MR	Mauritania
BF	Burkina Faso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GN	Guinea	NL	Netherlands
BJ	Benin	GR	Greece	NO	Norway
BR	Brazil	HU	Hungary	PL	Poland
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland	KR	Republic of Korea	SN	Senegal
CI	Côte d'Ivoire	LI	Liechtenstein	SU	Soviet Union
CM	Cameroon	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TG	Togo
DE	Germany	MC	Monaco	US	United States of America
DK	Denmark				

Microfabricated Device for Biological Cell Sorting

This invention relates to the sorting of biological cells into spatially separate sub groups. The criteria
5 for sorting may be applied to measurements obtained by any technique or techniques suitable for microfabricated or electronic implementation on a substrate.

Microfabrication and microelectronic techniques offer a
10 number of actual and potential measurement techniques that may be applied to characterize biological cells. Examples of these are microrheological measurements as disclosed in International Patent Application No. PCT/GB91/00289 and morphological measurements. When
15 suitably implemented such techniques can be applied on a cell by cell basis.

When characterizing a population of cells it can be of interest to workers to be able to isolate a sub
20 population whose measured parameters lie within certain bounds. This could enable, for example, the culturing of a cell line from sorted cells possessing a certain property or properties of interest.

25 We have discovered that recent developments in

microfabrication, namely the development of controlled, deflectable, microbeams capable of deflections in the order of a few micrometres, may be used to provide the component parts of microfabricated cell sorters.

- 5 Relevant microelectromechanical structures, and their formation by selective CVD techniques, are disclosed in: "Selective Chemical Vapor Deposition of Tungsten for Microelectromechanical Structures" by N.C. MACDONALD et al., Sensors and Actuators, 20 (1989) 123-133. The
- 10 so-called "microtweezers" are activated by control voltages applied to electrodes.

According to the current invention such a machine is implemented by utilising a microfabricated moveable

15 structure, preferably microfabricated beams, to direct cells between distinct spatial locations.

A particular implementation of the invention is shown in the drawing, which is a topological plan view of a

20 substrate on which a cell sorter is formed. In this example the cells to be sorted, whose diameters may be only a few micrometres, are fed sequentially from an entry port 1, via a guiding structure 2, past a generalised sensing device or zone 3. Depending upon the

25 result of the measurement and its interpretation the deflectable beams 4, 5, 6, are set into appropriate states to direct the cell into a particular destination,

for example, a hole 7, 8, 9 or 10 etched through the substrate. In the example shown the destination is structure 9. The beams, along with associated bifurcations can be extended to a tree structure of 'n' levels thereby yielding 2^n possible sorting sub ranges.

The absolute lengths of the channels are as short as possible while maintaining compatibility with interconnecting structures. The shafts 1, 3, 7-10 may be fabricated by selective etching as disclosed in the copending International Patent Application referred to above; the etched substrate is closed by a glass/silica cover, thereby forming the channels as tunnels.

Typical dimensions of the entry port 1 are 500 μ m or less square; of the sensing zone about 100 μ m square; of the channels about 5 to 10 μ m in width and depth; of the holes (shafts) 7 - 10 about 500 μ m or less square; and of the beams, which are typically of constant rectangular section, about 150 μ m long by 3 μ m square. The overall dimensions of the device could be 1cm square.

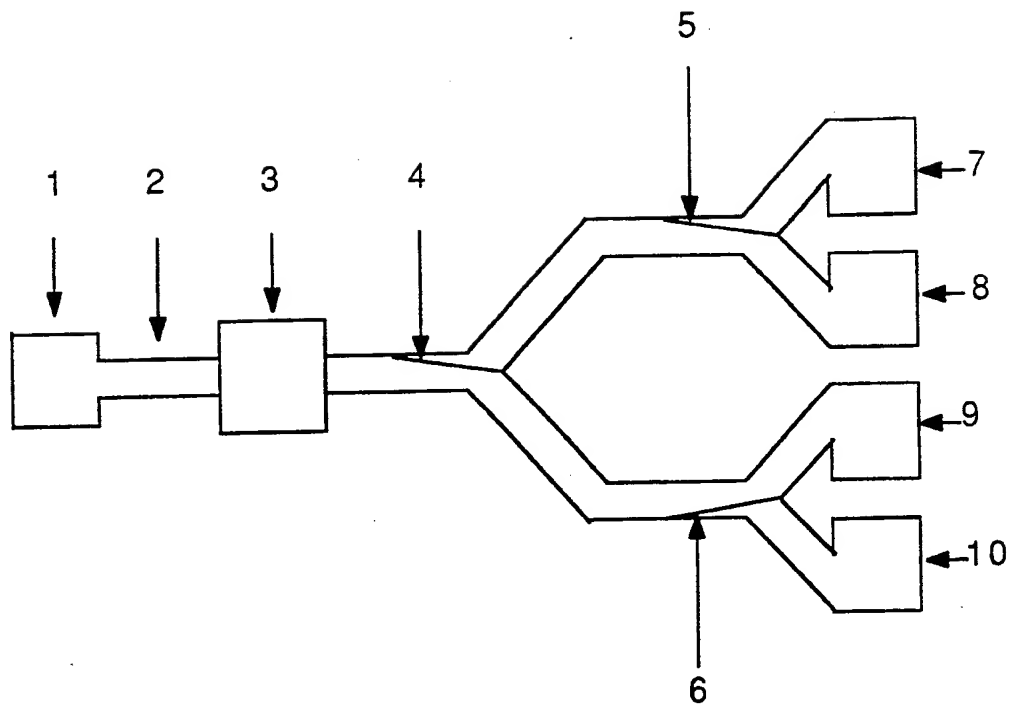
The beams are activated by selective control voltages applied as signals for control circuitry (not shown) operated, for example, under the control of a microprocessor or other computer. The computer is

programmed to control the beams' deflection in response to the desired cell-sorting procedural steps.

Claims:

1. Apparatus for sorting cells into spatially separate sub-groups, comprising a microfabricated moveable
5 structure (4, 5, 6) for directing cells between distinct spatial locations.
2. Method for sorting cells into spatially separate sub-groups, comprising directing the cells into distinct
10 spatial locations using a microfabricated moveable structure.

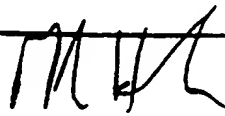
1/1.



INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 91/00542

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ^a		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. E	G01N15/14 ; G01N15/02 ; B07C5/34	
II. FIELDS SEARCHED		
Minimum Documentation Searched ^b		
Classification System	Classification Symbol	
Int.Cl. E	G01N ; B07C ; B01	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ^b		
III. DOCUMENTS CONSIDERED TO BE RELEVANT^c		
Category ^c	Citation of Document ^c with indication, where appropriate, of the relevant passage ^d	Relevant to Claim No. ^e
A	US.A.4 676 274 (JAMES F BROWN) June 30, 1987 see column 9, line 22 - line 56 see column 12, line 7 - line 60; figures 12,13 ---	1,2
A	REVIEW OF SCIENTIFIC INSTRUMENTS. vol. 51, no. 1, January 1980, NEW YORK US pages 111 - 115; P LENZ: 'Mechanical cell separator' see page 111 - page 113 ---	1,2
A	PROCEEDINGS OF THE IEEE. vol. 70, no. 5, May 1982, NEW YORK US pages 420 - 457; K E PETERSEN: 'Silicon as a mechanical material' see page 434 - page 435 see page 442 - page 443 see page 446 - page 449 ---	1,2
	-/-	
^a Special categories of cited documents : ¹⁰ ^{"A"} document defining the general state of the art which is not considered to be of particular relevance ^{"E"} earlier document but published on or after the international filing date ^{"L"} document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) ^{"O"} document referring to an oral disclosure, use, exhibition or other means ^{"P"} document published prior to the international filing date but later than the priority date claimed ^{"T"} later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention ^{"X"} document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step ^{"Y"} document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. ^{"&"} document member of the same patent family		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
12 JULY 1991	30.07.91	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	HOODSON C.M.T. 	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	EP,A,177 718 (PARTEC AG) April 16, 1986 ---	

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

GB9100542

SA 46699

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on

The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 12/07/91

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-4676274	30-06-87	EP-A- 0293519	07-12-88
EP-A-177718	16-04-86	CA-A- 1256825	04-07-89
		JP-A- 61137062	24-06-86
		US-A- 4756427	12-07-88

EPO FORM P0079

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

THIS PAGE BLANK (USPTO)

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☒ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.

THIS PAGE BLANK (USPTO)